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PATENT
Docket MZ 100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re: Application of : MICHAEL A. ZASLOFF ET AL

Serial No. 10/053,299 Examiner: Sheikh, Humera N.
Filed 01/17/2002 Art Unit: 1615
Title: METHODS AND COMPOSITIONS FOR BLOCKING MICROBIAL ADHERENCE TO EUKARYOTIC CELLS

CERTIFICATE OF MAILING

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Henry E. Millson, Jr.
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REPLY BRIEF TRANSMITTAL

Commissioner for Patents
P. O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Appellant's reply brief, in triplicate, is transmitted herewith in accordance with 37 CFR 1.193.

Respectfully submitted,

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REPLY BRIEF ON APPEAL UNDER 37 C.F.R.§ 1.193

Commissioner for Patents
P.O.Box 1450
Alexandria, Virginia 22313-1450

Sir:

This reply brief is in response to the EXAMINER'S ANSWER (Answer) mailed 04/05/2006.

It is noted that "The 35 U.S.C.§ 112, first paragraph rejection (Enablement and Written Description) has been withdrawn."

On page 4 of the Answer, the Examiner sets forth the teachings of the Pedersen patent. Applicant does not disagree with the Examiner's description of the invention disclosed by Pedersen.

This disclosure in the Pedersen patent is not, however, a disclosure of the present invention as set forth in claims 1-6, 8-16, 18, 25 and 41-44, which have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Pedersen.

Claim 1 and the rejected claims dependent thereon (claims 2-6,8-10 and 41-44) claim a method of blocking microbial adherence to a eukaryotic cell surface in a mammal by applying thereto a pharmacologically acceptable composition consisting essentially of an isoleucine stereoisomer or analog of isoleucine in a microbial blocking quantity. Isoleucine acts to block microbes from attaching to and thereby infecting eukaryotic cells.

The Pedersen invention uses metal chelates of amino acids in which it is the metal ion in the chelate that is the active ingredient of the composition, wherein the metal ion reacts with volatile sulfur compounds present in the oral cavity (see e.g. col. 3, lines 26-36; col. 5 lines 52-62; col. 6 lines 9-16; and col. 8, lines 9-12. Essentially any amino acid can be used to form the chelate (see e.g. col. 6, lines 17-39).

There is no disclosure in Pedersen that a particular amno acid, isoleucine, not in the form of a chelate with a metal ion, when applied to eukaryotic cells in a microbial blocking quantity can block microbes from attaching themselves to cell surfaces. There

is in fact no disclosure in Pedersen that any free amino acid alone can provide any beneficial effect when applied to eukaryotic cells. The Examiner in making the rejection of the presently claimed invention over Pedersen's disclosure, is in effect removing the metal ion from the chelates, despite Pedersen's clear teaching that it is the metal ion that is the effective ingredient in his compositions, and concluding that one skilled in the art would do so and assume that amino acids alone are effective in reacting with volatile sulfur compounds to prevent halitosis in the oral cavity, despite Pedersen's teachings to the contrary. There is clearly no such supporting disclosure in Pedersen. This is respectfully submitted to be a hindsight rejection using the present disclosure as a template. Moreover, the present invention still cannot result from this hindsght rejection, since where is there any teaching to select isoleucine from the disclosure that any amino acid can work in Pedersen's metal chelate invention, and where is any disclosure of the blocking effect of isoleucine when applied to cells, or the application thereof in a microbial blocking quantity to achieve this blocking effect?

At the bottom of page 4 and 5, the Examiner admits that Pedersen does not disclose the ranges of microbial blocking quantities but concludes that "it is not inventive to discover optimum of workable ranges by routine experimentation". However, these ranges relate to an entirely different invention from that disclosed by Pedersen, so this is an apples/oranges comparison. No case of prima facie obviousness exists since the inventions are unrelated.

On page 6 and 7 of the Answer, the Examiner refers to the possible presence of zinc ions in the presently claimed compositions. It is true that zinc ions can be present in the instant compositions, but only as a separate component, i.e. as part of a mixture of components. Chelates are not contemplated in the term "zinc ions". See e.g. col. 2, lines 43-46 of Pedersen where it is stated that "Furthermore, chelates are also referred to in the art as so called coordination compounds. The coordination compounds are very often slightly soluble, non-ionic complexes (underlining added). In the present description, the term "metal amino acid chelate" is used in this meaning." Hence, the presence of zinc ions in the present composition does not include the non-ionic coordination compounds (i.e. chelates) of the Pedersen reference.

On page 7 of the Answer, the Examiner contends that "the amino acids are present in the metal chelates" and are not merely reactants. The Examiner seems to be contending here that chelates are mixtures of amino acids and metal ions. The reference makes a clear distinction between chelates and mixtures. See e.g. col. 4, lines 17-26; and col. 4 lines 1-11 where chelate formation requires a "reaction" to produce a "resulting molecule" having a "two or three five membered hetercyclic ring structure". It is not understood how the Examiner can argue otherwise. See also page 249 of Havley's Condensed Chemical Dictionary, Eleventh Edition (copy attached) in which chelate is defined as "The type of coordination compound..." (underlining added).

Hence, it is respectfully submitted to be clear that Pedersen's chelates are in fact the reaction product of one or more amino acids and metal ions; and that the amino acids are not present in free form in the chelate compounds.

On page 8 of the Answer, the Examiner again refers to Pedersen's compositions as comprising "a metal ion, and an amino acid, such as isoleucine" and refers to the ABSTRACT. However, the ABSTRACT states that "The composition comprises a chelate comprising a metal ion, preferably a zinc ion, and an amino acid, preferably glycine." (underlining added). Read in the context of the rest of the disclosure, it is clear that this description is not meant to mean a mixture of a metal ion and an amino acid, but rather a reaction product (chelate) of a metal ion and an amino acid (see e.g. the above discussion).

The Examiner also contends that "It is the position of the Examiner that since beneficial, antimicrobial effects are attained using Pedersen's formulation, the amounts of amino acids present would also be a microbial blocking quantity as instantly claimed". Here again, Pedersen makes it clear that it is the metal in the chelate that provides the antimicrobial effect. See e.g. col. 8, lines 5-9 where it is stated that "However, by reacting with the sulphur-containing amino-acids in the oral cavity, the metal ion moiety of the chelate significantly reduces the microbial growth potential which in turn is likely to lead to a reduced plaque formation". There is no disclosure here (or elsewhere in the patent) that free amino acids not in the form of a reactant in chelates are prsent in Pedersen's compositions.

The Examiner's contentions on pages 8-9 with respect to ranges of microbial blocking quantities of isoleucine have been discussed above and in the appeal brief.

Concerning the Examiner's position with respect to claim 8, this claim relates to forms of the compositions of the invention, which are unrelated to Pedersen's compositions, and contain amounts of isoleucine which Pedersen does not disclose at all. Optimization of Pedersen's chelates does not optimize free amino acids, and clearly not the specific amino acid of the present invention.

With respect to claim 11 discussed by the Examiner on page 10 of the Answer, Pedersen discloses no free isoleucine amino acid component and therefore of course no quantities thereof, nor are the listed additional active substances present in combination with isoleucine.

Concerning claims 12 and 13, Pedersen does not disclose the quantities of isoleucine contained therein - his chelates contain no such free amino acid components.

Claim 18 recites a cell surface blocking quantity of isoleucine in a toothpaste or gel form. As stated in the appeal brief, Pedersen contains no such disclosures.

Claim 42 recites a quantity of isoleucine not disclosed by Pedersen. Pedersen does not teach a composition comprised of amino acids to impart antimicrobial properties. As discussed above, Pedersen discloses only metal chelates and teaches that chelates can reduce bacterial concentrations by reaction of the metal in the chelate with sulfur-containing components, in which the metal is the active component.

With respect to claim 44, Pedersen clearly does not recognize that any free amino acid can provide an antibacterial effect-his invention relates only to metal chelates wherein the metal is the active component used to treat halitosis. The amino acids are used to form the chelates and are not disclosed as having any other function.

Concerning the operating examples discussed on pages 11-14 of the Answer, in the Example 1 discussion the Examiner refers to the possible presence of zinc ions. As discussed above, a mixture of isoleucine and zinc ions is not a metal chelate of the reaction product of isoleucine and a zinc compound. It is respectfully submitted that the "consisting essentially of" language does exclude the metal chelates of Pedersen, since the metal chelates are distinct separate active compounds (which are not present in Example 1).

With respect to example 2, the Examiner contends that Pedersen teaches the incorporation of isoleucine in similar formulations. This contention is respectfully controverted. Pedersen teaches only chelates used for topical oral administration to control halitosis and the like. There is no teaching or suggestion that even Pedersen's metal chelates can be used to control diarrhea, and clearly no teaching that isoleucine itself can produce such a beneficial affect.

In Examples 3 and 4, discussed by the Examiner on pages 13 and 14 of the Answer, the Appellant is not just arguing that Pedersen does not show certain features of the present invention, but rather that Pedersen teaches no features of the present

invention. It is respectfully contended that the Examiner cannot arrive at the presently claimed invention without the use of hindsight, and in fact, not even then.

The discussion of the operating Examples by Appellant in the appeal brief was to further show the unobvious nature of the invention.

With respect to the operating examples, where is there any teaching or suggestion in Pedersen that his chelates can be ingested as in present Examples 2 and 3? For what purpose would his chelates be ingested? His chelates are used topically in the oral cavity to react with sulfur compounds to diminish halitosis. Where is any support for a conclusion that there are sulfur compounds in the GI tract that need to be reacted? Or that metal chelates are either safe or effective for ingestion? Also, even if ingested, this would be ingestion of metal chelates, which is not the present invention.

On page 14 of the Answer, the Examiner has rejected claims 1-13, 18, 25, 31, 32, 34 and 41-44 under 35 U.S.C. § 103(a) as being unpatentable over the Zeng reference. Zeng teaches a composition containing one or more of amino acids, physiologically acceptable salts of amino acids, obigopeptides and polypeptides to reduce vaginal acidity. Zeng also discovered that in high acidity vaginitis, accompanied by fungal vaginitis, by neutralizing the acidity with the above compositions not only reduced the high acidity, but this reduction in acidity also resulted in improvements in the fungal vaginitis, i.e. the reduction of acidity improved the fungal vaginitis as a secondary benefit.

As noted by the Examiner, the composition can also contain anti-fungal drugs to suppress and kill the fungi.

As discussed in the appeal brief, amino acids for effective neutralization of acidity in Zeng's patent are always present as mixtures of large numbers of amino acids.

The amino acid mixtures are used in amounts sufficient to neutralize the acidic vaginas. There is no teaching or suggestion in Zeng of using a single amino acid, isoleucine, to block cell surfaces to prevent adherence of microorganisms on the cell, nor any teaching of a microbial blocking quantity to obtain this result.

On page 15 of the Answer, the Examiner discusses the quantities of amino acid total contents to achieve the desired neutralization of acids in the acidic vaginas. The Examiner contends that these are overlapping amounts, reading on the instant ranges and amounts claimed. However, as discussed in the appeal brief, these amounts disclosed by Zeng are first of all mixtures of amino acids, and secondly are the amounts needed to neutralize acidic vaginas, not microbial blocking quantities. There is no basis for an assumption that sufficient quantities of the particular amino acid isoleucine will remain in the vagina after neutralization to provide a microbial blocking quantity.

Also, as admitted by the Examiner, Zeng does not teach the microbial blocking quantities set forth in claims 2-4, even for Zeng's neutralizing purposes using amino acid mixtures. The Examiner refers to optimum or workable ranges by routine experimentation. Since Zeng's compositions are neutralizing agents, how can ranges for an entirely different purpose for a single amino acid be optimized to arrive at the presently claimed quantities?

It is also not agreed that Zeng's formulations treat vaginitis. Zeng's neutralizing agents treat acidity, which neutralization has a secondary beneficial effect on fungal vaginitis. Neutralization using a mixture of amino acids is not a disclosure of treating fungal vaginitis, including non-acidic vaginas, by applying thereto a microorganism blocking quantity of isoleucine to cell surfaces. Here again it is respectfully contended that only through the use of hindsight can the teachings of Zeng be changed to use a particular amino acid, isoluceine, from a large mixture of amino acids, to block microorganism adherence to cell surfaces, using an effective blocking quantity thereof. Zeng clearly does not teach or suggest the presently claimed invention, nor does Zeng inherently disclose such an invention.

Where is there a teaching in Zeng that particular quantities of a particular amino acid, isoleucine, can be used for any purpose other than as a component of a mixture of amino acids for neutralizing acidic vaginas? Zeng's neutralizing agents are not even for use in nonacidic vaginas. There is also no disclosure in Zeng for the use of his amino acid mixtures in any other part of the body, and clearly no disclosure of using isoleucine alone to provide blockage of microorganism adherence to eukaryotic cells. Where does Zeng teach the use of isoleucine in cell surfaces blocking quantities?

Here again, it is respectfully submitted that Zeng's disclosure cannot render the present invention obvious absent a large infusion of hindsight.

At the top of page 18 of the Answer, the Examiner states that "Zeng clearly teaches that fungal conditions, such as fungal vaginitis can be treated using amino acids, which include isoleucine and L-forms of isoleucine."

This statement is not correct. The mixtures of amino acids are used by Zeng only to neutralize acidic vaginas, wherein such neutralization has a secondary beneficial effect on fungal vaginitis. See e.g. col. 6, lines 6-23. The mixtures of amino acids are not used to treat fungal vaginitis in nonacidic vaginas, which would be the case if they were disclosed as having separate anti-fungal activity.

On page 18 of the Answer the Examiner refers to the use of isoleucine in the amino acid mixtures in Zeng's compositions. As discussed above, the amino acid mixtures are used as neutralizing agents for acidic vaginas, which is not the presently claimed invention.

On page 19 of the Answer the Examiner contends that Appellant is limiting the teachings of Zeng to one particular example. Appellant discussed Example 1 since it was reasonably assumed, as noted in the appeal brief, that the Examiner was referring to this example.

In the paragraph at the bottom of page 19 and the paragraph at the top of page 20 of the Answer, the Examiner refers to the disclosure in Zeng of antifungal agents. Appellant is pointing out here that antifungal agents are needed to cure fungal infections in highly acidic vaginas, i.e. his amino acid neutralizing mixtures are not antifungal agents for the direct tgreatment of fungal infections. With respect to Appellant's

disclosure of anti-fungal agents, such agents may be needed to effect a complete cure in some cases of vaginitis, in which the isoleucine compositions of the invention would assist the anti-fungal agents to achieve a rapid cure.

In the middle of page 20 of the Answer the Examiner has interpreted the present claims as permitting mixtures of amino acids. However, as noted in the appeal brief, the present claims are limited to an amino acid component consisting of isoleucine stereoisomers or active analogs of isoleucine. The claims do not set forth or include the presence of other amino acids. It is not known whether or not the presence of other amino acids would interfere with the microorganism blocking effects of isoleucine, and the claims have been drafted to exclude such other amino acids.

In the two full paragraphs on page 21 of the Answer, the Examiner admits that the microbial blocking quantities set forth in claims 2-4 are not disclosed by Zeng, but asserts that the general conditions of the claims are disclosed in the prior art and therefore discovering optimum or workable ranges by routine experimentation would be obvious. However, the general conditions of the claims are not disclosed by Zeng whose invention relates to neutralizing agents. How can optimizing ranges for neutralizing agents relate to the discovery of cell blocking quantities of isoleucine to prevent attachment of microorganisms to the cells surfaces?

On page 22 of the Answer the Examiner contends that since Zeng teaches use of his neutralizing agents to produce a beneficial effect on fungal infecitons in highly acidic vaginas, his formulation would also reduce or alleviate the attachment of microbes such

as fungus. This assumption is first of all a hindsight conclusion, not taught or suggested by Zeng. Also, as discussed above, Zeng discovered that neutralizing highly acidic vaginas having fungal infections can produce a beneficial effect on the fungal condition. He does not assert or claim that amino acid mixtures can function as antifungal agents absent their action as neutralizing agents.

In the remaining half of page 22, the Examiner again refers to a pharmaceutical composition and method for treating vaginitis especially fungal vaginitis. As discussed above, Zeng teaches only the use of amino acid mixtures as neutralizing agents for highly acidic vaginas, which neutralization produces a beneficial effect on the fungal infection. This is not a teaching of any of the stated limitations in claim 1, and conclusions to the contrary can only be made using hindsight.

On pages 23 and 24 of the Answer the Examiner discusses claims 2-4, 11, 12-13, 18, 31, and 44. These claims have been discussed in the appeal brief and such discussion will not be repeated here.

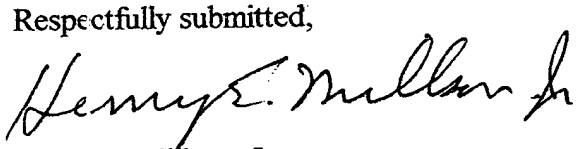
However. with respect to claim 44, the Examiner refers to a prior art patent for what it does not teach, and refers to col. 3, lines 44-50 for a statement that "amino acids, oligopeptides and polyseptides can change the metabolic process of bacteria and reduce acid production." Changing the metabolic process of bacteria to reduce acid production is not a statement of "effective treatment of bacterial conditions" as asserted by the Examiner. Changing metabolic processes of bacteria to produce less acid is clearly not a

statement that the bacterial can otherwise be killed or reduced in number. To produce less acid the bacteria must remain alive.

In conclusion, it is submitted that the claims on appeal set forth an unobvious invention not taught or suggested by either of the references.

Accordingly, the Board is respectfully requested to find for Appellant with respect to the issues.

Respectfully submitted,



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Condensed
Chemical
Dictionary
Eleventh Ed[illegible]

charcoal, wood. A highly porous form of amorphous carbon.
Derivation: Destructive distillation of wood.
Grade: Technical, in lumps, powdered, briquettes.
Hazard: Dangerous fire risk in briquette form or when wet, may ignite spontaneously in air.
Use: Chemical (precipitant in the cyanide process, precipitant of iodine and lead salts from their solutions, catalyst, calcium carbide); decolorizing and filtering medium; gas adsorbent; component of black powder and other explosives; fuel; arc light electrodes; decolorizing and purifying oils; solvent recovery; deodorant.

Chardonnet, H. (1839–1924) A native of France, he has been called the father of rayon because of his successful research in producing what was then called artificial silk from nitrocellulose. He was able to extrude fine threads of this semisynthetic material through a spinneret-like nozzle and the textile product was made on a commercial scale in several European countries. He was awarded the Perkin medal for this work.

Charles' Law. At constant volume, the pressure of a confined gas is proportional to its absolute temperature.
See also Gay-Lussac's Law.

Charpy. A standard testing device for impact strength.

chaulmoogra oil. (gynocardia oil; hydnocarpus oil).
Properties: Brownish-yellow oil or soft fat, characteristic odor, somewhat acrid taste. Soluble in ether, chloroform, benzene, solvent naphtha; sparingly soluble in cold alcohol; almost entirely soluble in hot alcohol, carbon disulfide. D 0.940, iodine value 85–105 (based on type) optically active.
Chief constituents: Glycerides of chaulmoogric and hydnocarpic acids.
Use: Medicine (treatment of leprosy and other infective skin diseases).

chaulmoogric acid. (hydnocarpyl acetic acid). $\overline{CH_2CH_2CHCHCH}(CH_2)_{12}COOH$. A cyclic fatty acid.
Properties: Colorless, shiny leaflets; mp 68.5C; soluble in ether, chloroform, and ethyl acetate.
Source: Chaulmoogra oil.
Use: Medicine, biochemical research.

chavicol. (p-allylphenol; 1-allyl-4-hydroxybenzene). $C_3H_5C_6H_4OH$.
Properties: Liquid, mp 16C, bp 230C, d 1.033 (18/4C), soluble in water and alcohol. Occurs in many essential oils.

CHDM. See 1,4-cyclohexanedimethanol.

checking. Development of small cracks in the surface of a material such as rubber, paint or ceramic glaze.

"Cheelox."[307] TM for a series of organic chelating and sequestering agents, consisting of polycarboxylic acid derivatives of amines or polyamines or their salts, i.e., ethylenediaminetetraacetic acid.

"Chel."[443] TM for chelating agents based on polyaminocarboxyllic acids.
Use: To reduce the harmful effects of trace metals.

chelate. The type of coordination compound in which a central metal ion such as Co^{2+}, Ni^{2+}, Cu^{2+}, or Zn^{2+}, is attached by coordinate links to two or more nonmetal atoms in the same molecule, called ligands. Heterocyclic rings are formed with the central (metal) atom as part of each ring. Ligands offering two groups for attachment to the metal are termed bidentate (two-toothed); three groups, tridentate; etc.
A common chelating agent is ethylenediaminetetraacetic acid (EDTA). Nitrilotriacetic acid $N(CH_2COOH)_3$; and ethyleneglycol-bis(β-aminoethyl ether)-N,N-tetraacetic acid $(HOOCCH_2)_2NCH_2CH_2OCH_2CH_2OCH_2CH_2N(CH_2COOH)_2$ are used in analytical chemical titrations and to remove ions from solutions and soils. Metal chelates are found in biological systems, e.g., the iron-binding porphyrin group of hemoglobin and the magnesium-binding chlorophyll of plants. Medicinally, metal chelates are used against Gram-positive bacteria, fungi, viruses, etc.
See also ammine, sequestration, complex, cobaltammine.

"Chelon."[428] TM for a series of chelating agents.

"Chem-Hoe."[177] TM for isopropyl-N-phenylcarbamate (IPC). A selective herbicide.

Chemical Abstracts. A weekly publication of the American Chemical Society which consists of research articles and patents in all major fields of chemistry throughout the world. It is the most indispensable publication in chemical literature and is the largest scientific abstract journal in the world. For further information, see Appendix II.

Chemical Abstracts Service. See chemical data processing.

chemical bond. See bond, chemical.